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Cardiovascular risk and metabolic syndrome in primary hyperparathyroidism and their correlation to different clinical forms

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Abstract

Cardiometabolic disorders have been associated with primary hyperparathyroidism (PHPT), while the relationship of cardiovascular risk score (CRS) and metabolic syndrome (MS) with different clinical presentation of PHPT remains undefined. Our aim was to evaluate CRS, MS and its components in PHPT looking for their correlation to different clinical forms. In 68 consecutive PHPT patients and 68 matched controls, CRS, MS and its components were assessed to perform an observational case–control study at an ambulatory referral center for Bone Metabolism Diseases. Patients were stratified in symptomatic and asymptomatic PHPT; these latter were divided in high-risk and low-risk subgroups for end-organ damage. An increased proportion of PHPT patients had intermediate-high CRS and MS (mean, 95 % Confidence Interval (CI) 51.5 %, 39.6–63.3 and 20.6 %, 11.0–30.2, respectively, $p < 0.02$ vs. controls). Intermediate-high CRS was prevalent both in symptomatic and low-risk asymptomatic PHPT while MS resulted prevalent in low-risk asymptomatic but not in symptomatic PHPT. Type 2 DM, IFG, mixed dyslipidemia, hypertriglyceridemia, HDL-hypocholesterolemia, and LDL-hypercholesterolemia predominated in low-risk asymptomatic, while only LDL-hypercholesterolemia prevailed also in symptomatic PHPT. In patients and controls without cardiometabolic risk factors, HOMA-IR index was significantly increased in PHPT vs. controls ($p < 0.03$) and associated to total calcium ($R = 0.73$; $p < 0.001$). By multivariate analysis low-risk asymptomatic PHPT predicted MS after adjusting for age, sex, and BMI. Our data show an increased frequency of intermediate-high CRS both in symptomatic and low-risk asymptomatic PHPT while MS prevails in low-risk asymptomatic PHPT, supporting the potential for cardiovascular morbidity and mortality also in this form.

Introduction

In primary hyperparathyroidism (PHPT), beyond the classical bone and stone manifestations, there is now evidence showing subtle cardiovascular and metabolic abnormalities, probably accounting for an increased morbidity and mortality [1–3]. Among cardiovascular alterations, increased arterial stiffness and carotid intima-media thickness, endothelial dysfunction, hypertension, left ventricular hypertrophy, and diastolic dysfunction have been reported [4, 5]. Among metabolic disorders, impaired insulin sensitivity, high prevalence of type 2 diabetes mellitus (Type 2 DM), dyslipidemia, hyperuricemia, increased body weight, and metabolic syndrome (MS) have been shown [6–12]. So far, it remains to be fully elucidated the pathogenetic link between PHPT and cardiometabolic morbidity and mortality which might be ascribed potentially to the contributory role of hypercalcemia, high serum PTH levels and vitamin D deficiency [4, 6, 13, 14] .

Clinical PHPT presentation is progressively shifting from a symptomatic disease, with kidney stones and/or overt bone disease and/or hypercalcemic crisis, to an asymptomatic disease without organ damage and mild hypercalcemia [15]. Moreover, according to the Third International Workshop on the management of asymptomatic PHPT [16], patients with asymptomatic form could be divided into two subgroups based on likelihood of long-term end-organ damage. Asymptomatic PHPT patients with one of the following characteristics including osteoporosis or fragility fracture, serum calcium levels higher than 1 mg/dl above the upper limit of normal range, age lower than 50 years, calculated glomerular filtration rate <60 ml/min should be considered at high risk for end-organ damage and referred for surgery, in the same way as symptomatic form, while the remainder of the asymptomatic patients, considered at low risk, could be followed up safely without surgical intervention.

Although an increased cardiovascular morbidity and mortality have been shown, there are until now no data about CRS in PHPT. Moreover, hypertension and metabolic alterations, known to be inter-related, have been investigated mostly separately and only few studies focusing on the prevalence of MS reported inconsistent findings about its size and relationship with different clinical presentation of PHPT [10, 11, 17].

The aim of the present study was to evaluate the prevalence of cardiovascular risk and altered glucose tolerance, dyslipidemia, hypertension, either separately or collectively as MS, in symptomatic and asymptomatic PHPT. Moreover, we looked for the association between these cardiometabolic abnormalities and biochemical indices of PHPT after adjusting for other clinical factors known to influence insulin resistance.

Patients and methods

Among subjects referred consecutively to our Bone Metabolism Diseases Centre, from 2005 to 2011, 68 patients with PHPT and 68 controls, completely assessed for cardiometabolic parameters, were recruited to perform an observational case–control study. The diagnosis of PHPT based on elevated serum calcium levels in the face of inappropriately high serum PTH levels. Controls were enrolled among patients with suspected osteoporosis: 31 had bone mineral density (BMD) Tscore in osteoporotic range, 25 in osteopenic range and 12 in normal range. Both patients and controls were on free Mediterranean diet with mild alcohol intake up to one drink a day for women or two drinks a day for men; they were able to perform normal daily living activities.

Exclusion criteria include patients with multiple endocrine neoplasia, Paget's disease, familial hypocalciuric hypercalcemia, secondary hyperparathyroidism, hypothyroidism, thyrotoxicosis, spontaneous or iatrogenic hypercortisolism, neoplastic diseases, and alcohol abuse. Controls were matched to PHPT patients for age (mean ± SD: 61.7 ± 13.5 vs. 64.8 ± 13.9 year; range ±5 years) and BMI (25.5 ± 4.3 vs. 25.2 ± 5.3 kg/m^2; range ±1 kg/m^2).

The patients were stratified into two groups, i.e., symptomatic and asymptomatic PHPT based on bone and/or stone disease and/or hypercalcemic crisis [15]. Moreover, asymptomatic PHPT patients were divided in two subgroups based on likelihood of long-term end-organ damage, according to guidelines on the management of asymptomatic PHPT stated in the Third International Workshop [16]: (a) patients with at least one of the following parameters, i.e., serum calcium >1.0 mg/dl above upper limit of normal range, BMD Tscore ≤ −2.5 at any site or fragility fracture, calculated glomerular filtration rate below 60 ml/min, and age <50 years (high-risk asymptomatic PHPT); (b) patients with hypercalcemia ≤1.0 mg/dl above upper limit of normal range, BMD Tscore > −2.5 at the three sites, calculated glomerular filtration rate ≥60 ml/min and age ≥50 years (low-risk asymptomatic PHPT).

Cardiovascular risk score (CRS) was estimated according to NCEP-ATPIII report [18]. Considering medical history, including specifically cardiovascular disorders and diabetes mellitus, as well as various cardiovascular risk factors such as age, sex, serum total, and HDL-cholesterol levels, systolic blood pressure and smoking habit, this report calculates a 10 years risk for hard coronary heart disease (CHD), that we expressed as low (<10 %) or intermediate-high (≥10 %).

Insulin resistance was calculated by means of homeostasis model assessment [19].

Diagnosis of diabetes and other categories of altered glucose tolerance, i.e., impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) were based on WHO criteria [20], while diagnosis of dyslipidemia and hypertension were based on NCEP ATP III criteria [18] and according to The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension and the European Society of Cardiology [21].

MS was defined according to the NCEP ATP III criteria [18], apart from using BMI as a surrogate for waist circumference to define visceral obesity (BMI ≥ 30 kg/m^2), as already done by other authors both in epidemiologic studies [22] and in clinical studies [23].

This study was performed according to the Declaration of Helsinki II and approved by the local Ethics Committee.

Serum total calcium (Ca, mmol/l) and phosphate (P, mmol/l) were tested using automated methods based on colorimetric and enzymatic assays (Cobas, Roche). For serum iCa (mmol/l), a specific probe was used after correction for pH. Serum intact PTH assay (pg/ml) based on an immunoradiometric sandwich method (IRMA) that used two polyclonal antibodies (DiaSorin): an antibody, recognizing the C-terminal region (aa 39–84) was used as the capture antibody while an antibody recognizing the N-terminal region was used for detection; inter- and intra-assay coefficient of variation were 5.5 % and below 3 %, respectively. Serum 25 OH vitamin D (ng/ml) was tested by a radioimmunoassay method using an antibody with specificity to 25-OH-D (DiaSorin). Serum insulin (μU/ml) was measured by a Solid-phase immunometric assay (Immulite, Siemens). The sensitivity of the insulin assay was 2 μU/ml while the intra and the inter-assay coefficients of variation were 4.0 and 4.9 %, respectively. Plasma glucose, serum total and HDL cholesterol, triglycerides and creatinine levels (mg/dl), were measured by enzymatic colorimetric tests (Cobas, Roche). LDL cholesterol was calculated using Friedewald's formula. Serum alkaline phosphatase (ALP, UI/l) was tested using colorimetric assay in accordance with a standardized method (Cobas, Roche): in the presence of magnesium and zinc ions, p-nitrophenyl phosphate was cleaved by phosphatases into phosphate and p-nitrophenol, proportional to the ALP activity that was measured photometrically. Serum bone alkaline phosphatase (BAP, ng/ml) was measured by an immunoradiometric sandwich method that use mouse monoclonal antibodies directed against two different epitopes of BAP and hence not competing (Beckman Coulter).

BMD was assessed by dual-energy X-ray absorptiometry on a Hologic QDR 4500 instrument (Bedford, MA, USA). BMD measurements are given as grams per square centimeter.

Data are presented as mean ± SD or as mean, 95 % confidence interval (CI). Normality of frequency distribution functions was tested by the Shapiro–Wilk *W* test. Significant differences were sought by the Mann–Whitney *U* test or Pearson's χ^2 analysis. Spearman's *R* coefficient was used to look for associations of calcium metabolism parameters with those of either glucose and lipid metabolism or hypertension. Logistic regression analysis was used to assess the relationship of clinical forms and biochemical indices of PHPT with metabolic disorders, hypertension and CRS; data are presented as odds ratios (OR) and 95 % CI, while pseudo R^2 expressed the amount of variance of dependent variable due to independent variables.

Calculations were performed using STATISTICA for Windows release 5.1; $p < 0.05$ was considered significant.

Results

Between PHPT patients and controls, there were no difference in sex distribution (M:F, 14:54 vs. 10:58), lumbar BMD (0.90 ± 0.16 vs. 0.84 ± 0.15 g/cm^2), femoral neck BMD (0.61 ± 0.07 vs. 0.64 ± 0.13 g/cm^2), femoral total BMD (0.72 ± 0.10 vs. 0.75 ± 0.15 g/cm^2), family history of Type 2 DM (frequency %, 95 % CI 5.9 %, 0.3–11.5 vs. 5.9 %, 0.3–11.5), family history of hypertension (10.3 %, 3.0–17.5 vs. 13.2 %, 5.2–21.3), family history of early-onset and late-onset coronary artery disease (1.5 %, 0–4.3 vs 1.5 %, 0–4.3 and 4.4 %, 0–9.3 vs. 4.4 %, 0–9.3, respectively), and smoking habit (10.3 %, 3.1–17.5 vs. 5.9 %, 0.3–11.5).

Age and BMI were not significantly different among various PHPT subgroups (age: 62.0 ± 14.0 vs. 66.3 ± 13.8 vs. 64.8 ± 16.2 vs. 68.0 ± 10.4 years and BMI: 25.5 ± 3.8 vs. 25.1 ± 5.9 vs. 24.9 ± 6.5 vs. 25.5 ± 5.1 kg/m^2 for symptomatic, asymptomatic, high-risk and low-risk asymptomatic PHPT, respectively).

Use of anti-hypertensive and antidyslipidemic drugs was more frequent in PHPT patients than in controls (frequency, 95 % CI 48.5 %, 36.7–60.4 vs. 27.9 %, 17.3–38.6, $p < 0.02$ and 19.1 %, 9.8–28.5 vs. 5.9 %, 0.3–11.5, $p < 0.02$, respectively). No difference between the two groups was found in the use of oral antidiabetic drugs; only 7 PHPT patients were treated with insulin. Frequency of hypertension was significantly higher ($p < 0.05$) in PHPT patients (whole group: 54.4 %, 42.6–66.3) and low-risk asymptomatic form (61.9 %, 41.1–82.7) than in controls (35.3 %, 23.9–46.7) while no differences were found in prevalence of cardiovascular disease (4.4 %, 0–9.3 vs. 2.9 %, 0–7.0).

The biochemical features of PHPT patients and controls are shown in Table 1. Serum PTH, ionized calcium, BAP levels and urinary calcium were significantly lower in asymptomatic than in symptomatic PHPT patients while serum 25 OH vitamin D levels were lower in symptomatic but not in asymptomatic PHPT than in controls.

Table 1. Biochemical features in patients with primary hyperparathyroidism and controls

	PHPT (whole group) *n* = 68	**Symptomatic PHPT *n* = 23**	**Asymptomatic PHPT *n* = 45**	**Controls *n* = 68**	**Normal ranges**
PTH (ng/l)	129.8 ± 77.2*	168.3 ± 95.3*	109.7 ± 57.5*,†	34.8 ± 17.1	10.0–65.0
Serum total calcium (mmol/l)	2.76 ± 0.18*	2.80 ± 0.22*	2.74 ± 0.15*	2.33 ± 0.11	2.20–2.60
Serum ionized calcium (mmol/l)	1.40 ± 0.13*	1.44 ± 0.14*	1.37 ± 0.11*,†	1.13 ± 0.24	1.10–1.30
Serum phosphate (mmol/l)	0.83 ± 0.15*	0.80 ± 0.15*	0.86 ± 0.15*	1.12 ± 0.20	0.80–1.40
Urinary calcium (mmol/die)	6.6 ± 4.5‡	9.4 ± 5.6*	4.8 ± 2.5†	4.1 ± 2.8	2.5–7.5
Urinary phosphate (mmol/die)	24.0 ± 9.5	26.6 ± 8.7	21.6 ± 9.8	24.3 ± 9.8	12.9–32.3
25(OH) vitamin D (nmol/l)	43.2 ± 25.2‡	35.2 ± 18.7‡	46.4 ± 27.0	57.4 ± 30.7	75.0–150.0
ALP (UI/l)	112.4 ± 57.2*	127.4 ± 68.0*	100.1 ± 44.5‡	72.1 ± 17.3	50.0–150.0
BAP (µg/l)	25.5 ± 19.2*	34.8 ± 22.8*	18.1 ± 12.0†,‡	10.5 ± 5.4	8.0–16.0
Serum creatinine (µmol/l)	70.7 ± 17.7	61.9 ± 8.8	79.6 ± 17.7†,‡	70.7 ± 17.7	44.2–106.1
Creatinine clearance (ml/s)	1.3 ± 0.5	1.4 ± 0.6	1.2 ± 0.4‡	1.4 ± 0.5	1.2–2.0

Data are presented as mean ± standard deviation and analyzed by Mann–Whitney test. * $p < 0.001$ vs controls; † $p < 0.05$ vs. symptomatic PHPT; ‡ $p < 0.05$ vs. controls

PHPT primary hyperparathyroidism

Excluding patients on antidiabetic therapy, plasma glucose levels were significantly higher in PHPT patients as a whole group, than in controls; they were also higher in asymptomatic (whole group) and low-risk asymptomatic but not in symptomatic PHPT patients (Table 2). Considering specific glucose tolerance alterations, enhanced frequency of Type 2 DM was shown in PHPT patients (whole group) and low-risk asymptomatic form; an increased frequency of IFG was shown only in low-risk asymptomatic PHPT patients, while the increased frequency of IGT in all forms of PHPT patients did not reach statistically significant difference (Fig. 1).

Table 2. Blood glucose and lipids levels in primary hyperparathyroidism patients and controls, excluding subjects on antidiabetic and antidyslipidemic drugs, respectively

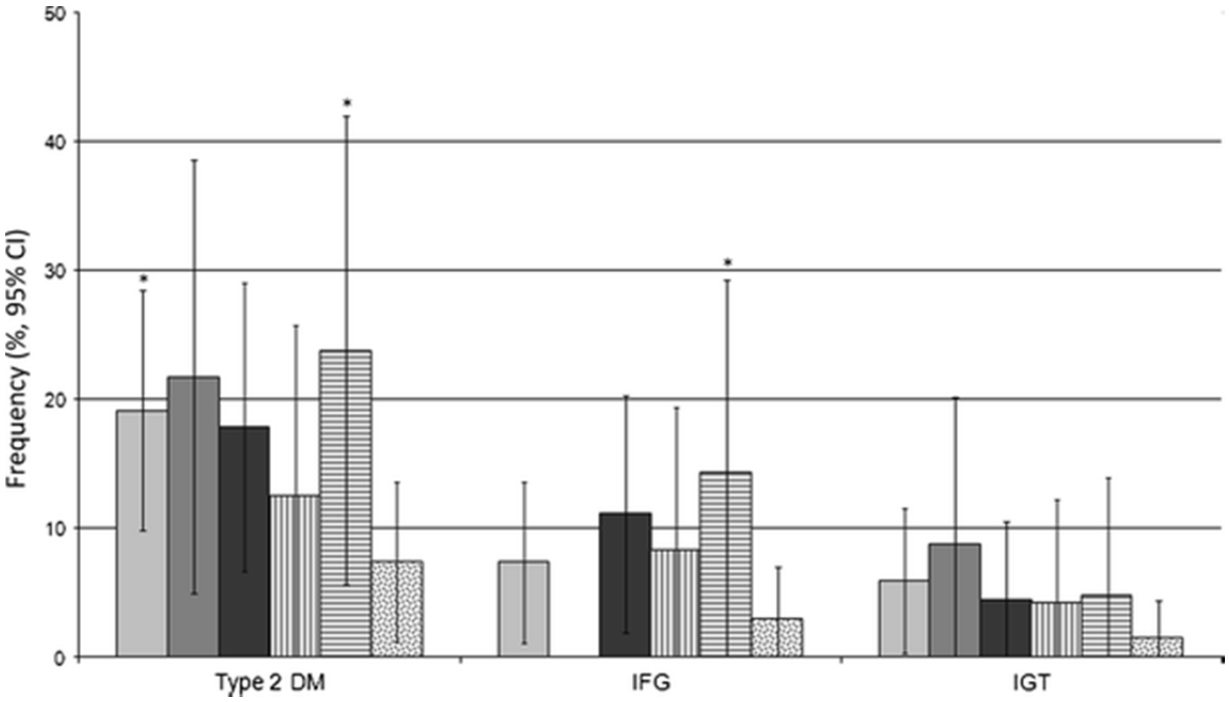
	PHPT (whole group) *n* = 56	Symptomatic PHPT *n* = 18	Asymptomatic PHPT (whole group) *n* = 38	High-risk asymptomatic PHPT *n* = 21	Low-risk asymptomatic PHPT *n* = 17	Controls *n* = 63
Glucose (mmol/l)	5.10 ± 0.90*	4.95 ± 0.54	5.17 ± 1.03*	5.05 ± 1.17	5.32 ± 0.83*	4.75 ± 0.62

	PHPT (whole group) *n* = 51	Symptomatic PHPT *n* = 18	Asymptomatic PHPT (whole group) *n* = 33	High-risk asymptomatic PHPT *n* = 17	Low-risk asymptomatic PHPT *n* = 16	Controls *n* = 64
Triglycerides (mmol/l)	1.31 ± 0.58*	1.26 ± 0.43	1.33 ± 0.65	1.05 ± 0.46	1.63 ± 0.71*	1.07 ± 0.45
Total cholesterol (mmol/l)	5.62 ± 1.10	5.84 ± 1.03*	5.50 ± 1.12	5.44 ± 1.00	5.56 ± 1.27	5.34 ± 0.83
HDL cholesterol (mmol/l)	1.55 ± 0.47	1.52 ± 0.47	1.56 ± 0.48	1.71 ± 0.49	1.42 ± 0.43	1.61 ± 0.40
LDL cholesterol (mmol/l)	3.47 ± 0.93	3.66 ± 0.91*	3.38 ± 0.94	3.37 ± 0.75	3.39 ± 1.12	3.22 ± 0.69

Data are presented as mean ± standard deviation and analyzed by Mann–Whitney test. * $p < 0.05$ vs. control

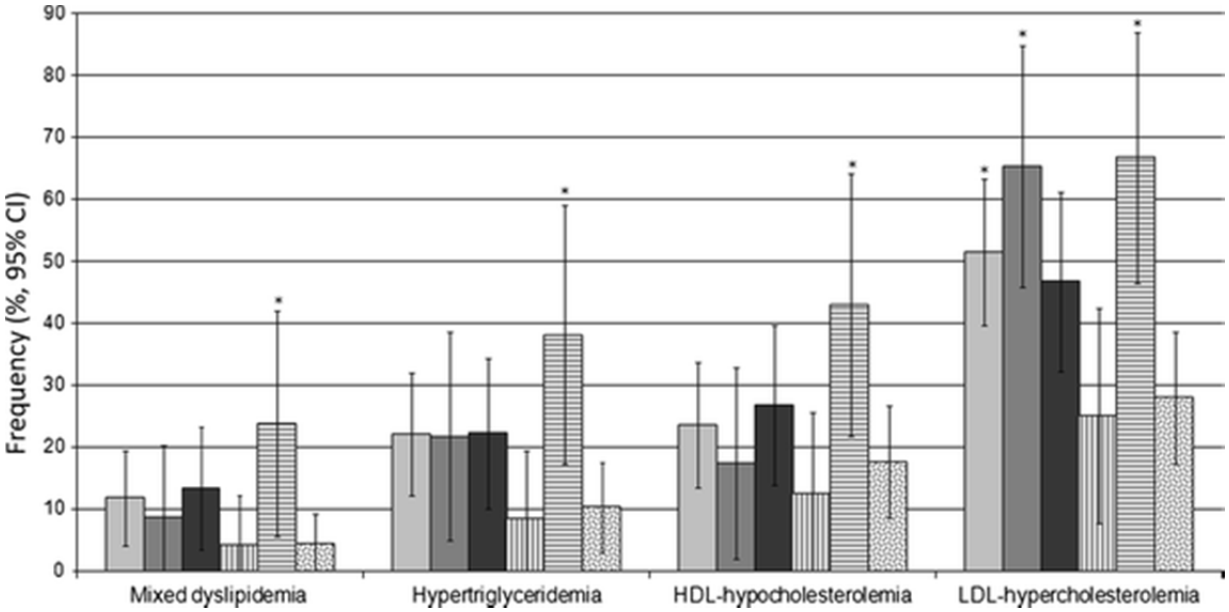
PHPT primary hyperparathyroidism

Figure 1



Frequency of Type 2 DM, IFG and IGT in PHPT patients, either as whole group, or according to different clinical forms and in controls. *Asterisk* denotes the significance level with respect to controls ($p < 0.05$)Excluding patients on antidyslipidemic drugs, triglycerides levels were higher in PHPT patients (whole group) and low-risk asymptomatic form than in controls. Total and LDL cholesterol levels were significantly higher only in symptomatic PHPT patients in comparison to controls (Table 2). An increased frequency of mixed dyslipidemia, hypertriglyceridemia, and HDL-hypocholesterolemia was shown only in low-risk asymptomatic PHPT patients. An increased frequency of LDL-hypercholesterolemia was present in PHPT patients (whole group) and symptomatic and low-risk asymptomatic forms (Fig. 2).

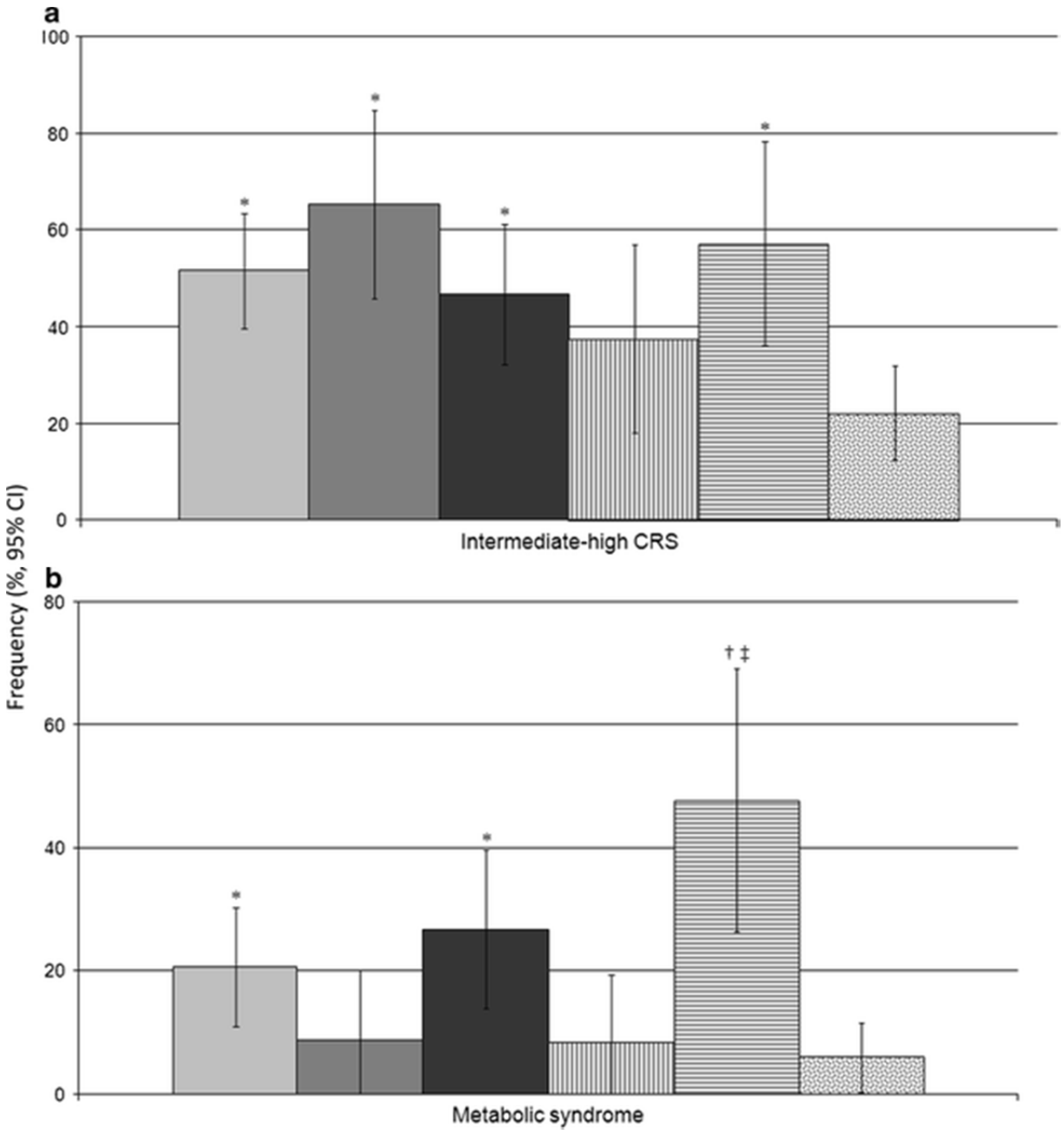
Figure 2



Frequency of mixed dyslipidemia, hypertriglyceridemia, HDL-hypocholesterolemia, and LDL-hypercholesterolemia in PHPT patients, either as whole group, or according to different clinical forms. *Asterisk* denotes the significance level with respect to controls ($p < 0.05$)

As shown in Fig. 3, intermediate-high CRS was found in an increased proportion of PHPT patients as whole group, in comparison to controls; frequency of intermediate-high CRS was also found higher in symptomatic, asymptomatic (whole group), and low-risk asymptomatic forms. Frequency of MS was higher in PHPT patients, as whole group, than in controls; it was found higher also in asymptomatic (whole group) and low-risk asymptomatic forms, but not in symptomatic patients; moreover, there was a prevalence of MS in low-risk asymptomatic in comparison to symptomatic and high-risk asymptomatic PHPT patients. When comparing PHPT patients with MS to those without it, the former showed lower total calcium levels (2.67 ± 0.11 vs. 2.78 ± 0.19 mmol/l, $p < 0.04$) and higher BMI (32.3 ± 5.3 vs. 23.6 ± 3.7 kg/m^2, $p < 0.001$).

Figure 3



Frequency of intermediate-high CRS (**a**) and metabolic syndrome (**b**) in PHPT patients, either as whole group, or according to different clinical forms and in controls. $*,^{\dagger}$ denotes the significance level with respect to controls ($p < 0.05$ and $p < 0.000005$, respectively); ‡ denotes the significance level with respect to symptomatic and high-risk asymptomatic PHPT ($p < 0.004$)

In PHPT patients and controls some metabolic parameters and blood pressure were related in univariate analysis to serum PTH and total calcium levels. Table 3 shows significant positive association between PTH and glucose levels as well as between total calcium and glucose, triglycerides, and LDL cholesterol levels.

Table 3. Univariate analysis of serum PTH and total calcium with metabolic parameters and systolic and diastolic blood pressure in primary hyperparathyroidism patients and in controls, excluding subjects on antidiabetic, antidyslipidemic, and antihypertensive drugs

	R	*p*
PTH and plasma glucose	0.26	<0.004
PTH and total cholesterol	0.15	NS
PTH and HDL cholesterol	0.00	NS
PTH and triglycerides	0.18	NS
PTH and LDL cholesterol	0.14	NS
PTH and SBP	0.11	NS
PTH and DBP	0.19	NS
Total calcium and plasma glucose	0.18	<0.05
Total calcium and total cholesterol	0.14	NS
Total calcium and HDL cholesterol	−0.08	NS
Total calcium and triglycerides	0.21	<0.03
Total calcium and LDL cholesterol	0.20	<0.05
Total calcium and SBP	0.17	NS
Total calcium and DBP	0.23	NS

Data are presented as Spearman's R coefficient and *p* value

SBP systolic blood pressure; *DBP* diastolic blood pressure

In nine patients and nine controls without altered glucose tolerance and cardiovascular risk factors, HOMA-IR index was significantly increased in PHPT in comparison to controls (2.8 ± 1.0 vs. 1.5 ± 1.3, $p < 0.03$) and associated to total calcium ($R = 0.73$, $p < 0.001$).

In a model of multivariate logistic regression analysis (pseudo $R^2 = 0.20$), serum calcium levels (OR, 95 % CI 2.5, 1.3–4.8) and BMI (1.1, 1.0–1.3) predicted altered glucose tolerance, after adjusting for age, sex, dyslipidemia, hypertension, and PTH. When considering PHPT clinical presentation, BMI (1.5, 1.2–1.9) and low-risk asymptomatic form (17.0, 2.4–121.7) predicted MS (pseudo $R^2 = 0.49$) after adjusting for age and sex.

Discussion

Present results show that PHPT patients, independently of clinical presentation, bear an enhanced intermediate-high CRS in comparison to controls; these new data are in accord with previous studies reporting an increased coronary artery and cerebrovascular morbidity in PHPT [3, 4, 12].

In PHPT patients we find also an increased frequency of hypertension, hyperglycemia, hypertriglyceridemia, and HDL-hypocholesterolemia considered both separately and collectively as MS, as well as LDL-hypercholesterolemia and mixed dyslipidemia. In line with these results, blood glucose, triglycerides, total and LDL cholesterol levels were significantly higher in PHPT patients. Univariate analysis indicates that PTH and total calcium levels are significantly associated with plasma glucose, while total calcium is associated with triglycerides and LDL cholesterol levels. These findings partially fit with those already reported by other authors [10, 11, 17, 24, 25], though only two [11, 25] compare results with a local control group. Noteworthy, among PHPT patients subgrouped according to clinical presentation only those with low-risk asymptomatic form have a higher frequency of MS in comparison to controls, differently from intermediate-high CRS. Moreover, patients with low-risk asymptomatic form display a frequency of MS (47.6 %) strongly higher than that observed in symptomatic (8.7 %) and high-risk asymptomatic (8.3 %) forms, in line with data reported by Tassone et al. [17], but in contrast with Luboshitzky et al. [11]. However, Tassone et al. [17] did not divide asymptomatic patients in two subgroups based on likelihood of

long-term end-organ damage. Similarly, hypertension, Type 2 DM, IFG, mixed dyslipidemia, hypertriglyceridemia, and HDL-hypocholesterolemia prevail only in low-risk asymptomatic PHPT patients.

Overall these results suggest that also the slight increase of serum calcium and PTH levels that nowadays characterizes most PHPT patients, is able to cause both metabolic and cardiovascular alterations. In this context, the finding that PHPT patients with MS show total calcium levels less high than those without it is in line with the assumption that cardio-metabolic alterations are not strictly related to the degree of hypercalcemia. Data showing that MS and some of its constituents, such as hypertension, hyperglycemia, hypertriglyceridemia, HDL-hypocholesterolemia display an increased frequency in low-risk asymptomatic but not in symptomatic and high-risk asymptomatic PHPT patients is difficult to explain, also considering that there is no difference in age and BMI between these PHPT forms. It could be hypothesized that some metabolic abnormalities paradoxically may be corrected in symptomatic PHPT form, probably due to systemic symptoms and signs such as debility, weight loss, weakness and detrimental effects on health of high calcium levels. It is also noteworthy that 12 out of 24 high-risk asymptomatic PHPT patients have serum calcium levels >1.0 mg/dl above upper limit of normal range.

The presence of cardiovascular and metabolic alterations also in asymptomatic PHPT patients at low-risk for end-organ damage, suggests to investigate these disorders accurately in all patients with PHPT. On the other hand, these findings support a risk for cardiovascular morbidity and mortality in low-risk asymptomatic PHPT at least not lower than in symptomatic PHPT [2, 3, 12]. Consistently, also normocalcemic PHPT has been associated to metabolic and cardiovascular abnormalities [26, 27]. These data are in line with recent consideration of MacFarlane et al. [28] who suggest that “mild PHPT,” that commonly refers to individuals not meeting the NIH criteria for parathyroidectomy, should be reclassified as an insidious disease. Therefore, our results indicate that low-risk asymptomatic patients should be assessed and properly treated also by parathyroidectomy, just like symptomatic and high-risk asymptomatic PHPT.

In PHPT patients, a recent study reported an improvement of MS after surgery [25], while contradictory results have been reported on the efficacy of parathyroidectomy on glucose intolerance, insulin resistance and dyslipidemia [7, 29–31]. An amelioration of blood pressure after surgery has been found by some Authors [25] but not by others [2]. It could be hypothesized that PHPT could induce over many years structural vascular abnormalities; therefore parathyroidectomy could be effective only if performed in early phase of disease.

Present findings, in agreement with results of other Authors [6, 11, 32, 33], have also shown that insulin resistance is significantly increased in PHPT patients without altered glucose tolerance and cardiovascular risk factors; this increased insulin resistance probably leads over many years to metabolic disorders, hypertension, and to increased cardiovascular morbidity and mortality. Noteworthy our data show a positive correlation between serum total calcium levels and insulin resistance. Consistently, recent studies do not find an increased insulin resistance in patients with normocalcemic PHPT [34, 35]. However, it has to be underlined that cytosol calcium content seems more important than serum calcium to influence insulin secretion and sensitivity [36].

On the other hand, our finding, showing a positive association between serum PTH and plasma glucose levels, suggests a contributory role of PTH in cardiovascular risk of PHPT patients, as also confirmed by recent reports [4, 37].

25OH vitamin D deficiency could also play a role in cardiovascular risk of PHPT patients [14]. However, in our results 25OH vitamin D levels are lower in symptomatic but not in asymptomatic PHPT patients than in controls, suggesting that 25OH vitamin D deficiency does not seem to be an important contributory factor in cardiovascular risk. This hypothesis is in agreement with a recent study [38] which indicates a significant association of vitamin D status with all-cause mortality but not with ischemic heart disease or stroke.

Finally, results obtained by models of multivariate logistic regression analysis confirm the above-reported negative effect of PHPT on cardio-metabolic alterations showing that PHPT status predicts the presence of intermediate-high CRS and MS, while elevated calcium levels predict altered glucose tolerance among the components of MS.

Our study has some limitations. First, we studied a small sample of PHPT patients so that the proportion of patients with intermediate-high CRS and the figure of prevalence of MS and its components should be confirmed in larger studies. Second, we did not measure waist circumference so that the prevalence of MS could be underestimated using the criterion of BMI ≥ 30 kg/m^2 to define visceral obesity, although it has already been used in both epidemiological and clinical studies [22, 23].

In conclusion, our data in PHPT show that the increased frequency of intermediate-high CRS and MS connote also low-risk asymptomatic PHPT, supporting the potential for cardiovascular morbidity and mortality also in this form and indicating a not so strictly link to the degree of hypercalcemia. Moreover, surprisingly, frequency of MS in low-risk asymptomatic PHPT patients results even higher than in symptomatic and high-risk asymptomatic form. Therefore, PHPT patients should be assessed, beyond renal and bone damage, also for cardiovascular and metabolic disorders, that could be considered additional criteria for surgery in low-risk asymptomatic form of PHPT. Randomized control studies of the effect of early parathyroidectomy are required to definitely clarify the cause-effect relationship between altered

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